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Impact of COVID-19 vaccination in post-COVID cardiac complications

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ABSTRACT

Background: After the acute infection, COVID-19 can produce cardiac complications as well as long-COVID persistent symptoms. Although vaccination against COVID-19 represented a clear reduction in both mortality and ICU admissions, there is very little information on whether this was accompanied by a decrease in the prevalence of post-COVID cardiac complications. The aim of this study was to analyze the relationship between COVID-19 vaccination and the prevalence of post-COVID cardiac injury assessed by echocardiogram, and long-COVID persistent cardiac symptoms. **Methods**: All patients who consulted for post-COVID evaluation 14 days after discharge from acute illness were included. Patients with heart disease were excluded. The relationship between complete vaccination scheme (at least two doses applied with 14 days or more since the last dose) and pathological echocardiographic findings, as well as the relationship of vaccination with persistent long-COVID symptoms, were evaluated by multivariate analysis, adjusting for age, sex and clinical variables that would have shown significant differences in univariate analysis. **Results**: From 1883 patients, 1070 patients (56.8%) suffered acute COVID-19 without a complete vaccination scheme. Vaccination was associated with lower prevalence of cardiac injury (1.35% versus 4.11%, adjusted OR 0.33; 95% CI 0.17–0.65, p=0.01). In addition, vaccinated group had a lower prevalence of persistent long-COVID symptoms compared to unvaccinated patients (10.7% versus 18.3%, adjusted OR 0.52; 95% CI 0.40–0.69, p<0.001). **Conclusion:** Vaccination against COVID-19 was associated with lower post-COVID cardiac complications and symptoms, reinforcing the importance of fully vaccinating the population.

1. Introduction

The COVID-19 disease caused by the SARS-CoV-2, the seventh of its kind capable of infecting the human race [1], has produced more than 6.7 million deaths to date with around 660 million cases worldwide [2]. The clinical manifestations of COVID-19 range from mild respiratory symptoms, to severe pulmonary and systemic involvement [3]. Cardiovascular risk factors, advanced age, and preexisting diseases have shown to be predictors of worse clinical outcomes, increased admission to intensive care units (ICUs), and mortality [4–5]. Unlike other respiratory viral infections, COVID-19 is known to produce long-lasting symptoms or sequelae during convalescence, including respiratory, cardiac or neurological complications, among others [6–8]. Although the reported prevalence of this syndrome known as long-COVID are highly variable, some publications reported up to 90% of persistent symptoms up to 6 months after the acute infection [9]. Long-COVID syndrome is defined as "signs and symptoms that develop during or after a COVID-19 infection, and continue for more than 4 weeks, and cannot be explained by another cause" [10]. Several studies have demonstrated the ability of the SARS- CoV-2 to cause cardiovascular impairment, both indirectly and directly, and the pathophysiological mechanisms are now better established [8]. In addition to cardiovascular complications in the acute stage [12–13], there is a higher incidence of cardiovascular injury in the convalescent stage or post-COVID [7–8,14–15]. In a recently published study, our working group demonstrated a prevalence of cardiac injury in the convalescent stage of 4.8%, being more frequent in those patients with more severe acute conditions, and unrelated to long-COVID symptoms [16]. Since the start of mass vaccination for the SARS-CoV-2, a clear reduction in both mortality and ICU admissions has been observed [17–18]. However, there is very little information in the literature on whether this reduction in serious events related to vaccination was also accompanied by a decrease in the prevalence of post-COVID cardiovascular impairment or persistent symptoms.

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The primary objective was to analyze the relationship between COVID-19 vaccination and the prevalence of cardiac complications in the convalescent stage of infection. As a secondary objective, the relationship between vaccination and long-COVID persistent cardiac symptoms was analyzed.

2. Material and methods

Design: Observational, analytical and prospective study, developed in an outpatient cardiology center. The sampling was non-probabilistic and consecutive.

Inclusion and exclusion criteria: All patients who consulted for post-COVID evaluation 15 days after discharge from acute illness were included. Unvaccinated patients were included between 01st September 2020 and 30th June 2022. On the other hand, vaccinated patients were recruited between 29th December 2020 and 30th June 2022, as COVID-19 vaccines became available in Argentina after this date. Patients with another known or possible cause of heart disease were excluded: ischemic-necrotic, hypertrophic, restrictive, or dilated cardiomyopathy, severe valve disease, or any other relevant heart disease.

For the diagnosis of COVID-19, the case definition of the Ministry of Health of the Argentine Republic [19] was used. The population was divided according to whether or not they had received a complete vaccination scheme before suffering from the acute COVID-19. Complete vaccination was considered to be the scheme of at least two doses applied with 14 days or more since the last dose [20]. The vaccines available in Argentina at the time of the study were: platform messenger RNA, non-replicative viral vector and inactivated live virus [21].

Anamnesis included the presence of long-COVID cardiac symptoms, considering as such: dyspnea, palpitations, precordial discomfort and/or asthenia, not previously reported. A transthoracic echocardiogram (TTE) was performed in all the patients. Findings compatible with post-COVID cardiac injury were considered the presence of previously unknown: left ventricular ejection fraction (LVEF) $\leq$52% in men or $\leq$54% in women, regional wall motion abnormalities, or pericardial effusion. The value postulated by the American Society of Echocardiography (ASE) was used as a cut-off point to indicate LVEF deterioration, in order to increase its specificity [22].

Statistical analysis: Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables as percentages. For normally distributed variables, the analysis was performed using the Student's test. For non-normally distributed variables, the Wilcoxon rank sum test was used. Categorical data analysis was performed using the chi-square test or Fisher's test. The relationship between complete vaccination scheme and pathological echocardiographic findings, as well as the relationship of vaccination with persistent long-COVID symptoms, were evaluated by multivariate analysis, adjusting for age, sex and clinical variables that would have shown significant differences in univariate analysis. Statistically significant was defined as a value of p<0.05 (two-tailed test). For the statistical analysis, the STATA 13 program (Stata Corp, College Station, TX) was used.

Ethical considerations: The study protocol was reviewed and approved by the Ethics Committee of the Institution. The research was conducted in accordance with the declaration of Helsinki. All study participants gave their informed consent to participate in it, and their information was kept anonymous.

3. Results

In total, 1,883 patients (mean age 42±14.5 years, 46% men) were included. The mean time between diagnosis of COVID-19 and consultation was 62 days (range 16–330 days). 56.8% (n=1070) of the patients suffered acute COVID-19 without being fully vaccinated and 43.2% (n=813) after a complete scheme. The baseline characteristics and cardiovascular risk factors of the population are detailed in Table 1.

55 patients (2.92%) presented previously unknown pathological TTE findings consistent with post-COVID cardiac injury, including

Table 1
Baseline population characteristics. Compiled table outlining the most relevant baseline characteristics and cardiovascular risk factors in each group, according to vaccination status.

	Unvaccinated (N=1070)[a]	Vaccinated (N=883)[b]	p=
Age, years (mean ± SD)	42.1 (14.3)	42.3 (14.8)	0.765
Male sex (%)	48.5	43.8	**0.04***
BMI (mean ± SD)	26.1 (4.9)	26.5 (5.9)	0.432
Hypertension (%)	16.7	10.5	**<0.001***
Diabetes (%)	4.6	3.2	0.129
Dyslipidemia (%)	18.6	17.3	0.483
Smoking/former smokers (%)	14.9	8.5	**<0.001***

SD= standard deviation; BMI= Body Mass Index.
* significantly different (p < 0.05).
[a] 09/2020–06/2022.
[b] 12/2020–06/2022.

Table 2
Echocardiographic findings. Compiled table outlining the most relevant echocardiographic findings including those compatible with post-COVID cardiac injury in each group, according to vaccination status.

	Unvaccinated (N=1070)[a]	Vaccinated (N=883)[b]	p=
DD LV, mm (mean ± SD)	46.1 (4.8)	45.5 (4.8)	**0.02***
SysD LV, mm (mean ± SD)	27.8 (4.5)	28.3 (3.9)	**0.01***
Shortening fraction (mean ± SD)	0.40 (0.07)	0.41 (0.08)	0.131
Septum, mm (mean ± SD)	9.2 (1.7)	8.5 (1.5)	**<0.001***
Posterior wall, mm (mean ± SD)	8.2 (1.4)	7.7 (1.2)	**<0.001***
Left atrium area, cm^2 (mean ± SD)	16.9 (3.2)	16.7 (3.2)	0.103
Ejection fraction, % (mean ± SD)	64.0 (5.6)	63.9 (4.6)	0.761
Mitral E wave, m/s (mean ± SD)	0.80 (0.19)	0.84 (0.19)	**<0.001***
Mitral A wave, m/s (mean ± SD)	0.60 (0.18)	0.62 (0.19)	0.138
Post-COVID total injury findings, % (n)	4.1 (44)	1.35 (11)	**<0.001***
Pericardial effusion, % (n)	0.65 (7)	0.86 (7)	0.605
LV Systolic dysfunction, % (n)	2.9 (31)	0.37 (3)	**<0.001***
Wall motion abnormalities, % (n)	0.93 (10)	0.25 (2)	0.06

DD= Diastolic Diameter; LV= Left Ventricle; mm= millimeters; SD= standard deviation; SysD= Systolic Diameter; m/s= meters/seconds.
* significantly different (p < 0.05).
[a] 09/2020–06/2022.
[b] 12/2020–06/2022.

Table 3
Univariate and Multivariate analysis. Compiled table outlining univariate and multivariate analysis for outcomes of cardiac complications and long-COVID persistent cardiac symptoms. The multivariate model adjusted the variable of interest for age, sex, and risk factors that showed significant differences in the univariate analysis between the groups (hypertension and smoking).

Variable	Cardiac complications		Long-COVID persistent cardiac symptoms	
	OR (95% CI)	aOR (95% CI)*	OR (95% CI)	aOR (95% CI)*
Complete vaccination	0.32 (0.16–0.62)	0.33 (0.17–0.65)	0.53 (0.41–0.70)	0.52 (0.40–0.69)
Age	1.02 (0.99–1.04)	1.02 (0.99–1.04)	1.02 (1.01–1.02)	1.01 (1.00–1.02)
Male sex	2.42 (1.37–4.30)	2.29 (1.28–4.08)	0.62 (0.48–0.81)	0.58 (0.44–0.76)
Hypertension	2.23 (1.20–4.15)	1.44 (0.72–2.86)	1.81 (1.31–2.5)	1.54 (1.07–2.22)
Smoking	1.63 (0.81–3.28)	1.15 (0.56–2.38)	1.56 (1.09–2.12)	1.22 (0.85–1.76)
Diabetes	0.91 (0.22–3.80)	–	1.44 (0.80–2.56)	–
Dyslipidemia	1.42 (0.75–2.67)	–	1.44 (1.06–1.95)	–
Body mass index	0.99 (0.93–1.06)	–	1.04 (1.01–1.07)	–

aOR= Adjusted Odds Ratio.
*Complete vaccination adjusted for age, sex hypertension and smoking.

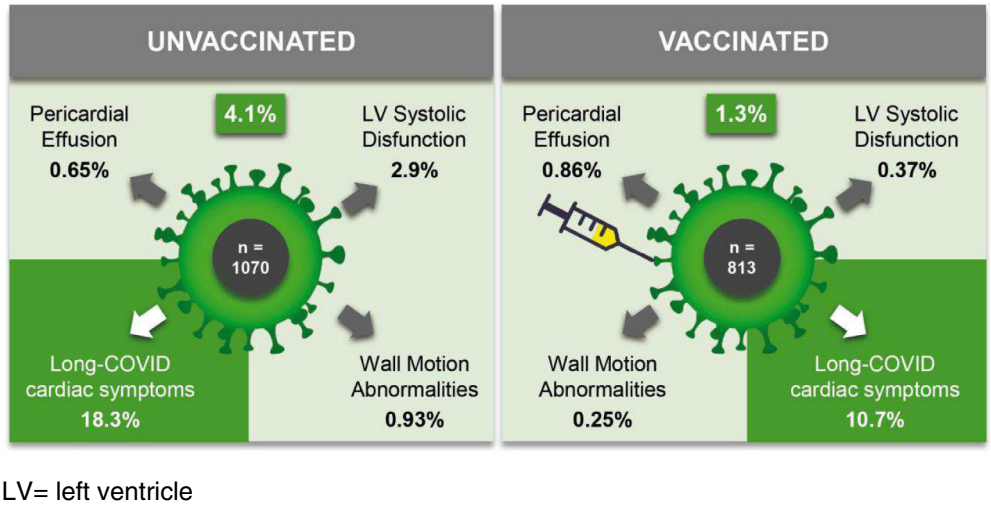

Fig. 1. Prevalence of post-COVID cardiac complications in unvaccinated and vaccinated populations. Prevalence of echocardiographic pathological findings compatible with post-COVID cardiac injury and persistent long-COVID symptoms in each group. Buenos Aires, 2020–2022.

left ventricular dysfunction (1.8%), pericardial effusion (0.74%) and wall motion abnormalities (0.64%). The echocardiographic data and the specific findings of cardiac injury in each group are detailed in Table 2. Globally, patients who had acute COVID-19 with a complete vaccination schedule had a lower prevalence of cardiac injury compared to unvaccinated patients (1.35% versus 4.11%, respectively, p<0.001). This association was maintained after adjusting for age and other cardiovascular risk factors (aOR 0.33; 95% CI 0.17–0.65, p=0.01). Univariate and Multivariate analysis in Table 3. Globally, 15% of the patients reported persistent symptoms at the time of the post-COVID control. Those patients in the fully vaccinated group had a lower prevalence of persistent long-COVID symptoms compared to the unvaccinated group (10.7% vs 18.3%, respectively, p<0.001), and this association was again maintained in the multivariate analysis (aOR 0.52; CI 95% 0.40–0.69, p<0.001) (Table 3).

Main results of prevalence of post-COVID cardiac complications are illustrated in Fig. 1.

4. Discussion

Our work reveal for the first time in our region that complete vaccination scheme was significantly associated with a lower prevalence of cardiac injury and fewer persistent cardiac long-COVID symptoms. The tropism of the SARS-COV-2 for the cardiovascular system has been widely demonstrated [7–8,11–15]. The most described mechanisms are direct virus-mediated cytotoxicity, down-regulation of ACE-2 receptors, hypercoagulability, endothelial damage, and immune-mediated inflammation [23–24], which can result in heart failure, myocarditis, pericarditis, infarcts secondary to thrombosis or hypoxia, autonomic dysfunction, arrhythmias, among others [7,25–26]. These cardiovascular manifestations can occur in the acute stage of the disease or during the post-COVID convalescence phase. Initial studies in 2020 demonstrated a very high incidence of post-COVID cardiovascular compromise, with some reports of up to 78% findings in control cardiac magnetic resonance (CMR) [27]. More than two years of experience and a clearly lower cardiac compromise rate in daily practalice put those initial results into discussion. More recent studies, such as the systematic review by Barssoum et al., have shown a much lower prevalence of pathological findings (3 to 5%) [28]. These results are similar to those found by our group, both in the first study prior to the start of the vaccination campaign (4.8% cardiac injury) [16] as in this study (2.9%).

Mass vaccination against COVID-19 infection has shown a clear reduction in adverse events in the acute stage [17], however, there is insufficient evidence on its effectiveness in reducing cardiovascular complications in the convalescent stage. A large-scale multicenter retrospective study concluded that vaccination for COVID-19 results in a reduction in "new cardiovascular events", referring to any type of cardiac pathology, whether myocardial infarction or

hypertension, as well as diabetes, thyroid disease, among others [29]. Similar, another large-scale retrospective study using national healthcare database from US shows that, beyond the first 30 days after infection, individuals with COVID-19 are at increased risk of cardiovascular events, including ischemic heart disease, arrhythmias, heart failure, thromboembolic events, among others. In a sub-analysis performed to eliminate the putative contribution of vaccine exposure to the outcomes of myopericarditis, the results suggested that COVID-19 was still associated with myopericarditis events [7]. However, to the best of our knowledge, no publication to date has directly related vaccination with a reduction in post-COVID cardiac injury as evidenced by imaging. A recent study by Puntmann et al prospectively assessed 349 previously healthy patients who experienced mild COVID-19, with blood biomarkers measurement and CMR. 144 patients received one dose of vaccine between the baseline and the follow-up CMR, and no differences were found between vaccinated and not vaccinated groups. Nevertheless, this study was performed in a highly selected, low risk and healthy population, and the sub-analysis was not the main objective of the study, limiting the possibility to draw conclusions [8].

In relative terms, our study showed that patients who had an acute case of COVID-19 without having received a complete vaccination schedule, showed three times more frequently cardiac injury than vaccinated patients, regardless of risk factors and patient's age. Regarding the secondary objective of our study (relationship of vaccination with persistent post-COVID cardiac symptoms), it should be noted that the long-COVID syndrome refers to the persistence of symptoms, regardless evidence of organ damage. The mechanisms by which recovery is prolonged in some patients seems to be related mainly to the patient's cardiovascular risk factors, sex and age, and not only to the severity of the acute COVID infeccion. [10,30–31]. Some of the postulated mechanisms are persistent viremia due to a weak antibody response, viral relapse or reinfection, inflammatory and immune reactions, physical deconditioning, and mental factors such as post-traumatic stress [30]. A recent systematic review, although with great heterogeneity, demonstrated a positive relationship between vaccination and the reduction in the incidence of new long-COVID symptoms, as well as an improvement of symptoms in those who already experienced them [32]. Other studies, on the contrary, report no relationship and even an increase in symptoms after vaccination [33–34]. In our work and in line with previous studies, although 15% of the patients reported post-COVID cardiovascular symptoms, pathological findings were only observed on the echocardiogram in 2.9% of the patients. Complete vaccination scheme was clearly and independently associated with a 48% reduction in the risk of persistent post-COVID cardiovascular symptoms.

On the other hand, there is evidence in the real world of myocarditis secondary to vaccination, although this was not an adverse event reported in the pivotal randomized studies of the different vaccines [35–38]. Large-scale studies have already shown that the incidence of myopericarditis secondary to COVID-19 infection is much higher than that secondary to vaccination [7,39], so it is agreed that the benefits of vaccination far outweigh the risks. This matches with our study, where patients in the pre-vaccination group had a higher prevalence of echocardiographic findings compatible with myopericarditis, compared to the group with complete vaccination.

Finally, it should be noted that the reduction in pathological findings in TTE and persistent symptoms in our study could be linked not only to vaccination, but also to other aspects not evaluated, such as the development of natural immunity, as well as the circulation of less virulent variants. Epidemiological data from the National Ministry of Health show that COVID-19 pandemic in Argentina has developed in 3 main peak circulation waves, each one with inner characteristics: the first one from August to December 2020, with the greater lethality because of the absence of COVID-19 vaccines. The second wave was the longer one, from March to August 2021, but with lower lethality rates because of the initiation of the vaccination campaign. Finally, the third wave from December 2021 to February 2022 was the one with the higher rates of contagion, but with lethality rates lower than 0.1%, with more than 75% of the population with complete vaccination scheme [40,41].

Our study has some limitations. First, given the observational design of our research, biases and confounders could be present. The fact that the patients from both groups were included at different historical moments could particularly bias the results of our work, mainly due to issues related to natural immunity or the type of circulating viral variant. However, epidemiological data from the National Ministry of Health shows that the predominant viral variant did not substantially changed in the period of time analyzed [42]. Second, we do not have information on the type of vaccine received by the patient (live attenuated virus or messenger RNA), although previous studies have not shown that this modifies the prevalence of post-COVID cardiac complications [34]. Although we had no reports of vaccine-related myocarditis in our charts, we cannot completely exclude this issue. Nevertheless, reports of myocarditis induced by COVID-19 vaccination are extremely low in literature [39]. The definitions of "case", "complete vaccination" and "post-covid syndrome" have changed throughout the course of the pandemic. This study used the current definitions at the time of carrying out the protocol, based on the recommendations of the Ministry of Health of Argentina Finally, due to the socioeconomic characteristics of the population that regularly attends our center, patients could have a better and closer control of their health, which could contribute to selecting a less sick population.

5. Conclusions

Complete vaccination scheme for COVID-19 was associated with a lower prevalence of post-COVID cardiac complications as well as long-COVID cardiac symptoms during convalescence. Our findings reinforce the importance of fully vaccinating against COVID-19.

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Data availability

The data that has been used is confidential.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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